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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,756	04/14/2006	Kenji Sasaki	P28062	5026
7055 7590 12/16/2008 GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191				
EXAMINER GUSLOW, ANNE				
ART UNIT		PAPER NUMBER		
1643				
NOTIFICATION DATE		DELIVERY MODE		
12/16/2008		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary

Application No.

10/539,756

Applicant(s)

SASAKI ET AL.

Examiner

ANNE M. GUSSOW

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 and 19-21 is/are pending in the application.
- 4a) Of the above claim(s) 2-4 and 19-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 5-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SI-108)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1, 5-9, and 19 have been amended.

Claim 18 has been canceled.

Claims 2-4 and 19-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 14, 2008.

2. Claims 1 and 5-17 are under examination.
3. The following Office Action contains NEW GROUNDS of Rejection.

Rejections Withdrawn

4. The rejection of claims 1 and 5-18 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment to the claims.
5. The rejection of claims 5 and 6 under 35 U.S.C. 102(a) as being anticipated by Kouno, et al. is withdrawn in view of applicant's arguments.

6. The rejection of claims 1, 5-11, and 13 under 35 U.S.C. 102(b) as being anticipated by Kunicki, et al. is withdrawn in view of applicant's amendment to the claims.
7. The rejection of claims 1 and 5-10 under 35 U.S.C. 102(b) as being anticipated by Thompson is withdrawn in view of applicant's arguments and the new grounds of rejection below.
8. The rejection of claims 1 and 5-17 under 35 U.S.C. 102(b) as being anticipated by Hosokawa, et al. is withdrawn in view of applicant's amendment to the claims.
9. The rejection of claims 1 and 7-18 under obviousness type double patenting over claims 11, 13, and 15 of copending application 10/497,516 is withdrawn in view of the cancellation of the claims of copending application 10/497,516.

Rejections Maintained/NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
11. Claims 1 and 5-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claims 1 and 5-18 are indefinite for reciting "adding a compound which has a disulfide bond in the molecule" in claims 1 and 5-9. It is not clear if the molecule is the same as the compound or if it is a different molecule. For the purposes of this office action the molecule and compound are interpreted as being the same compound.
- b. Regarding claims 16 and 17, the phrase "represented by" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. The rejection of claims 1 and 7-18 under 35 U.S.C. 102(a) as being anticipated by Kouno, et al. is maintained. The rejection of claims 5 and 6 is withdrawn in view of applicant's arguments, see 5 above.

The response filed May 20, 2008 has been carefully considered but is deemed not to be persuasive. The response states that, applicants respectfully submit that Kouno does not teach at least one element of the presently claimed invention, i.e., adding a compound which has a disulfide bond in the molecule. Applicants note that cysteine is not a compound possessing a disulfide bond. Applicants respectfully note the difference between the α -amino acid cysteine and cystine, a molecule comprising a

disulfide bond and disclosed in the present application as one of the preferred stabilizing compounds (see response page 7).

In response to this argument, applicant's dependent claims require the limitation of cysteine (see for example claims 8 and 9) as the compound which has a thiol group and exerts no influence on the activity of the protein, thus Kouno reads on the claim because Kouno administers cysteine and the claims require the addition of cysteine.

Therefore after a fresh consideration of the claims and the evidence provided, the rejection is maintained.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 and 5-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kouno, et al. (US PG PUB 2005/0123532, published June 9, 2005, as cited in the previous office action) in view of Thompson (US PAT 5130418, issued July 14, 1992, as cited in the previous office action).

The claims recite a method for protecting a thiol group in a protein having a free cysteine residue and wherein the protein is produced by using a cell cultured in a serum-free medium, which comprises comprising adding a compound which has a disulfide bond in the molecule and exerts no influence on the activity of the protein, wherein the compound which has a disulfide bond in the molecule and exerts no influence on the activity of the protein is cystine, homocystine, lipoic acid or oxidized glutathione. A method for protecting a thiol group in a protein having a free cysteine residue, which comprises adding a compound which has a disulfide bond in the molecule and exerts no influence on the activity of the protein simultaneously or

separately from a compound which has a thiol group in the molecule and exerts no influence on the activity of the protein, wherein the compound which has a thiol group in the molecule and exerts no influence on the activity of the protein is cysteine, homocysteine, glutathione or dihydrolipoic acid, wherein the protein is a recombinant protein, wherein the protein is an antibody, wherein the antibody is an F(ab')₂ antibody, wherein the antibody is a monoclonal antibody, wherein the monoclonal antibody has a thiol group in its variable region, wherein the monoclonal antibody has a free cysteine residue in its variable region, wherein the monoclonal antibody comprises the amino acid sequences represented by SEQ ID NOs: 1, 2 and 3 in the Sequence Listing in its heavy chain hypervariable region, and the amino acid sequences represented by SEQ ID NOs: 4, 5 and 6 in the Sequence Listing in its light chain hypervariable region, wherein the monoclonal antibody comprises a heavy chain variable region comprising the amino acid sequence represented by SEQ ID NO:7 in the Sequence Listing and a light chain variable region containing the amino acid sequence represented by SEQ ID NO:8 in the Sequence Listing.

Kouno, et al. teach a method for producing a protein having a free cysteine in serum free medium. Kouno, et al. teach the method carried out in the presence of a reducing agent (cysteine) having capacity low enough not to reduce the disulfide linkage in the protein molecule but high enough to reduce the free cysteine, wherein the protein is a recombinant protein, wherein the protein is a monoclonal antibody, wherein the protein is the F(ab')₂ fragment of the antibody. Kouno, et al. teach the use of a GAH antibody in the method. The GAH antibody has the CDR sequences of SEQ ID Nos. 1-

6 of the instant application and the variable region sequences of SEQ ID Nos. 7 and 8 of the instant application. Kouno, et al. teach no deterioration of the binding activity of the antibody after the steps of the method (example 12). Kouno, et al. do not teach addition of a compound which has a disulfide bond. This deficiency is made up for in the teachings of Thompson.

Thompson teaches a method for treating recombinant bFGF protein with organic disulfides, specifically either glutathione disulfide or cysteine, which enhanced stabilization of the protein molecule (see examples 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the protein having a free cysteine in serum free medium of Kouno, et al. using the organic disulfides as taught by Thompson.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the protein having a free cysteine in serum free medium of Kouno, et al. using the organic disulfides as taught by Thompson because Thompson teaches that protective agents (i.e. organic disulfides) can be any moiety which forms a covalent disulfide bond with the sulfhydryl of a free cysteine in the substrate protein to be stabilized (see column 5 lines 16-56). One of ordinary skill in the art would have known to substitute the instantly claimed cystine molecule for the cysteine of Kouno, et al. because Thompson teaches that any compound that can form a disulfide bond would function in the method. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention

was made to have produced the protein having a free cysteine in serum free medium of Kouno, et al. using the organic disulfides in view Thompson.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. The rejection of claims 1 and 7-18 on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1, 3, 10, 12, 14, 16, and 17 of copending Application No. 10/497,516 is maintained.

The response filed May 20, 2008 has been carefully considered but is deemed not to be persuasive. The response states that applicants respectfully submit that KOUNO does not teach at least one element of the presently claimed invention, i.e., adding a compound which has a disulfide bond in the molecule. Applicants note that cysteine is not a compound possessing a disulfide bond. Applicants respectfully note the difference between the α -amino acid cysteine and cystine, a molecule comprising a disulfide bond and disclosed in the present application as one of the preferred stabilizing compounds (see response page 7).

In response to this argument, as set forth above (see 13 above) applicant's dependent claims require the limitation of cysteine (see for example claims 8 and 9) as the compound which has a thiol group and exerts no influence on the activity of the protein, thus Kouno reads on the claim because Kouno administers cysteine and the claims require the addition of cysteine.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Claims 1 and 7-18 directed to an invention not patentably distinct from claims 1, 3, 10, 12, 14, 16, and 17 of commonly assigned Application No. 10/497,516. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/497,516, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

20. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
December 4, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643